APPENDIX A:
Update of Potency Factors for Lung Cancer (KL) and Mesothelioma (KM)

Estimates of risk of dying of lung cancer or mesothelioma from asbestos exposure are quantified by means of mathematical models that express risk as a function of exposure. The models utilized in the 1986 EPA Airborne Asbestos Health Assessment Update (USEPA, 1986) contain parameters (KL for lung cancer and KM for mesothelioma) that gauge the potency of asbestos for causing these health effects. USEPA calculated KL and KM values from a number of studies. In this section these KL and KM calculations are revised using the same models as in the EPA 1986 update, but incorporating newer data from more recent publications. Since the 1986 update, additional cohorts have been studied from several new exposure settings, and the followup periods have been extended for several of the previously studied cohorts.

In the 1986 update KM values were not calculated from all of the available studies, perhaps owing to the limited number of mesotheliomas observed in some of these studies. In this update, an attempt has been made to utilize any study with suitable health and exposure data, regardless of the number of mesotheliomas reported, and to quantify the statistical uncertainty attributable to small numbers using statistical confidence limits. Since the present work utilizes somewhat different methods from the 1986 update, for consistency, all of the KL and KM values were recalculated, even from studies for which no new data were available. Table 1 contains a summary of these new KL and KM calculations. The original values from the 1986 update are also provided for comparison.

Lung Cancer Model

The 1986 EPA lung cancer model (USEPA, 1986) assumes that the relative risk, RR, of mortality from lung cancer at any given age is a linear function of cumulative asbestos exposure (fiber-years/ml, or f-y/ml, as measured by PCM), omitting any exposure in the most recent ten years. This exposure variable is denoted by CE_{10}. The ten-year lag embodies the assumption that exposure does not influence lung cancer mortality until ten years has elapsed. The mathematical expression for this model is

$$RR = 1 + KL*CE_{10}, \qquad (1)$$

where the linear slope, KL, is the "lung cancer potency factor." Sometimes allowance is made for the possibility that the background lung cancer risk in the exposed population differs from that of the comparison population by applying the expanded model,

$$RR = \alpha(1 + KL*CE_{10}). \qquad (2)$$

With this form of the model the relative risk at zero exposure is α rather than 1.0. Both

KL and α are estimated by fitting the model to data. The type of data most appropriate for applying this model are from cohort studies in which observed and expected (based on an appropriate comparison population, e.g., U.S. males) numbers of lung cancers are categorized by cumulative exposure incorporating a ten-year lag. To explore the adequacy of the model, it is useful to have the data cross-classified by one or more other variables, such as latency.

Frequently the cumulative exposure variable available from the published report of a study does not incorporate a lag (or, less frequently, incorporates a lag of less than ten years). In this report, rather than attempting an *ad hoc* correction, no correction for lag has been made. Although this tends to cause KL values to be slightly underestimated, this is unlikely to be a serious problem. For most cohorts, exposures decreased significantly over time. Also, in many studies, followup didn't begin until several years after the start of exposure, and the bulk of the lung cancers occurred at older ages. All of these factors tend to mitigate the error created from use of data with no lag. Moreover, use of an *ad hoc* correction for lag could hinder comparisons of KL values among studies that do not employ a lag (which includes the majority of studies).

Mesothelioma Model

The 1986 EPA mesothelioma model (USEPA, 1986) assumes that the mortality rate at time t after the beginning of exposure can be calculated by summing the contributions from exposure at each increment of time, du, in the past. The contribution to the mortality rate at time t from exposure to E(u) f/ml (as measured by PCM) at time u is assumed to be proportional to the product of the exposure rate, E(u), and $(t - u - 10)^2$, the square of the elapsed time minus a lag of ten years. Thus, as with the lung cancer model, the mesothelioma model assumes a ten-year lag before exposure has any effect upon risk. With the additional assumption that the background rate of mesothelioma is zero, the mesothelioma mortality rate at time t since the beginning of exposure is given by

$$I_M(t) = 3 * KM * \int_0^{t-10} E(u) * (t - u - 10)^2 \, du, \qquad (3)$$

where t,u are in years, $I_M(t)$ is the rate per year at year t after the beginning of exposure, and the proportionality factor, KM, is the "mesothelioma potency factor." The factor of "3" is needed to retain the same meaning of KM as in USEPA (1986).

If exposure is at a constant level, E, for a fixed duration, DUR, this model can be written as

$$I_M(t) = \begin{cases} 0 & 0 \le t \le 10 \\ KM*E*(t - 10)^3 & 10 \le t \le 10 + DUR \\ KM*E*[(t - 10)^3 - (t - 10 - DUR)^3] & t \ge DUR \end{cases} \quad (4)$$

The genesis of this model and its agreement with data was discussed in USEPA (1986).

Through the courtesy of Dr. Corbett McDonald, Professor Douglass Liddell, Dr. Nicholas DeKlerk, and the National Institute for Safety and Health (NIOSH), raw data on mesothelioma mortality were obtained from a cohort of Quebec chrysotile miners and millers (McDonald *et al.*, 1980a; Liddell *et al.*, 1997), a cohort of Wittenoom, Australia crocidolite miners and millers (Armstrong *et al.*, 1988; DeKlerk *et al.*, 1994), and a cohort of workers from a plant Charleston, South Carolina that manufactured textiles from chrysotile (Dement *et al.*, 1983a,b, 1994; Dement and Brown, 1998). These data were used to calculate KM values in a more accurate manner (using the "exact" approach described below) for these cohorts, and to explore the potential magnitude of the errors incurred by the crude application of cohort-wide averages when fitting the mesothelioma model.

Statistical fitting methods

The method of maximum likelihood (Cox and Oakes, 1984; Venzon and Moolgavkar, 1988) was used herein to fit the lung cancer and mesothelioma models to data and to estimate KL and KM. The profile likelihood method was used to calculate statistical confidence intervals, and likelihood ratio tests were used to assess goodness-of-fit and test hypotheses.

Typically the data for calculating a lung cancer potency factor, KL, consist of observed and expected (based on an external control group, such as U.S. males) numbers of cancer deaths categorized by cumulative exposure. The likelihood of these data is determined by assuming that the deaths in different exposure categories are independent and the number of deaths in a particular category has a Poisson distribution with expected number given by the expected number predicted by the control group times the relative risk given by either expression (1) or (2).

In the typical situation, the published data most useful for calculating the mesothelioma potency factor, KM, consist the number of mesothelioma deaths and person-years of observation categorized by time since first exposure. The likelihood of these data is determined by assuming statistical independence of the number of mesothelioma deaths in different categories, and that the number of mesothelioma deaths in a category has a Poisson distribution with mean equal the number of person-years in the category times expression (4), using average values for E, DUR, and t appropriate for that category.

The fitting of the mesothelioma model (3) to raw mesothelioma data was accomplished using an "exact" maximum likelihood method. The cumulative mesothelioma hazard was defined as

$$H(t) = \int_0^t I_M(u)\,du. \qquad (5)$$

The contribution to the likelihood of a person whose followup terminated at t was $S(t) = 1 - exp(-H(t))$ if the followup did not terminate in death from mesothelioma, and $I_M(t)S(t)$ if the person died of mesothelioma. The complete likelihood was defined as the product of these individual contributions. The integrals in expressions (3) and (5) were evaluated numerically.

Selection of a "best estimate" of KL and KM

For each study for which a KL or KM was estimated, a "best estimate" was developed. For mesothelioma, this estimate was generally the maximum likelihood estimate derived from the best-fitting model in the form (3) for raw data and (4) for published data. For lung cancer, the best estimate of KL was generally assumed to be the maximum likelihood (MLE) estimate obtained with $\alpha = 1$ if this model fit the data adequately and the hypothesis $\alpha = 1$ could not be rejected. If this hypothesis could be rejected and the model with α estimated fit adequately, the MLE from this model was generally used as the best estimate. If neither model fit adequately, or if the result of the hypothesis test of $\alpha = 1$ was marginal, the geometric mean of the MLE with $\alpha = 1$ and α estimated was generally used as the best estimate. In other cases these general rules had to be adapted to fit the particular form of the data available.

Uncertainty in KL and KM

Statistical uncertainty in KL and KM estimates is expressed using statistical confidence limits. However, other sources of uncertainty, such as model uncertainty and uncertainty in exposure, are likely to also be very important. Although non-statistical uncertainties are difficult to quantify, it is important to attempt quantification, since presentation of statistical uncertainty alone may provide a misleading picture of the reliability of the estimates. Consequently, an ad-hoc approach to quantifying non-statistical uncertainty was adopted in this report. In this approach, a few general sources of uncertainty are identified. For each study, a factor for each uncertainty source was selected using loose guidelines. The individual factors were combined with the statistical confidence bounds to arrive at a "likely range" for KL or KM for each particular cohort. A "best estimate" within the range is also provided for each cohort.

The most serious uncertainties are often related to exposure. Air samples may not exist for certain departments or periods of time. Sampling was often sparsest in the

more distant past when exposures were generally highest. Often samples were not collected routinely and the context of historical samples may no longer be known. (E.g., were they representative, or were they worst-case?) Some asbestos jobs involved short and infrequent, but extremely dusty, conditions that were difficult to evaluate. In some studies historical exposure levels were estimated from samples collected during an attempt to recreate past exposure conditions. An uncertainty factor, F1, was selected for each study to reflect uncertainty in KL and KM estimates stemming from these issues. This factor is at least 1.5 and is 2 or greater in most cases.

Samples from the 1960's and earlier were collected using an impinger or similar apparatus that counted particles rather than fibers, and a conversion factor must be used to convert from, say, particle concentrations in million particles per cubic foot (mppcf) measured by an impinger to fiber concentrations in fibers per milliliter (f/ml) measured by phase contrast microscopy (PCM). Since different operations had different degrees of dustiness, a common conversion factor may not be appropriate for different cohorts or even for different jobs within the same plant. Some studies had available side-by-side samples by impinger and PCM, or concurrent samples collected over a period of years in different operations, which could be used to determine appropriate conversion factors for different operations. Other studies only had samples collected by an impinger, and no conversion factor was estimated. An uncertainty factor, F2, is used to represent the uncertainty in the conversion factor.

Some studies had highly variable working conditions, with little or no sampling data, and exposure levels were estimated from attempts to recreate typical working conditions. Other studies did not have individual work histories, and a crude estimate of average duration was applied to all members of the cohort. A third uncertainty factor, F3, is used to account for these special conditions.

In addition to uncertainty related to exposure, there are non-statistical uncertainties stemming from 1) lack of information on potential confounders, 2) questionable appropriateness of the comparison population, and 3) incomplete or inaccurate mortality ascertainment. Many studies do not have information on smoking, an important potential confounder for lung cancer. In some studies a sizable proportion of the cohort was loss to followup. Mesothelioma deaths were sometimes misclassified on death certificates as due to other types of cancer. To handle the appropriateness of the comparison population for lung cancer, the reported lower (upper) confidence bound selected was the smaller (larger) of the two bounds calculated with the background parameter, α, in the lung cancer model (2) estimated, and with this parameter fixed at $\alpha = 1$. Since all three non-statistical uncertainties imply an improper control population, this approach addresses to some extent all three problems. In addition, when it was deemed to be warranted, an additional non-exposure-related uncertainty factor for lung cancer, F4L, and/or mesothelioma, F4M, was proposed.

In addition to upper and lower statistical confidence intervals, four uncertainty factors have been proposed: F1: Exposure, general; F2: exposure conversion factor; F3: lack of individual work histories; F4L (lung cancer), F4M (mesothelioma): non-exposure related. Since it is unlikely that all of the uncertainty sources caused errors in the same direction, rather than multiplying the uncertainty factors, an overall uncertainty factor, F, was calculated as $F = \exp\{[Ln^2(F1) + Ln^2(F2) + Ln^2(F3) + Ln^2(F4)]^{½}\}$, where 1.0 is the default value for any factor not explicitly provided. The overall "reasonable range" for KL or KM was calculated by dividing the statistical lower bound by F and multiplying the upper bound by F.

Analysis of Individual Studies

Predominately Chrysotile Exposure

Quebec Mines and Mills

Liddell *et al.*, 1997 extended the followup into 1992 of a cohort of about eleven thousand workers at two chrysotile asbestos mines and related mills in Quebec that had been studied earlier by McDonald *et al.*, 1980 (followup through 1975) and McDonald *et al.* 1993 (followup through 1988). Production at the mines began before 1900. The cohort consisted of workers who worked one month or more and who were born between the years of 1891 and 1920. Follow-up began for each individual after 20 years from first employment. The most recent followup (Liddell *et al.*, 1997) traced 9780 men through May 1992, whereas 1138 (10%) were lost to view, most of whom worked for only a few months prior to 1935. Of those traced, 8009 (82%) were deceased as of 1992.

Estimates of dust levels in specific jobs were made from some 4,000 midget impinger measurements collected systematically starting in 1948 and periodically in the factory beginning in 1944. Estimates for the period prior to 1949 utilized interviews with long-term employees and comparison with more recent conditions. These dust-level estimates were matched to individual job histories to produce estimates of cumulative exposure for each worker (mppcf-years). Conversions between dust levels and PCM concentrations were derived from side-by-side samples. On the basis of over six hundred side-by-side midget impinger and optical microscopy measurements, it was estimated that 3.14 fibers/ml was, on the average, equivalent to 1.0 mppcf (McDonald et al., 1980b).

Liddell *et al.* (1997) categorized cancer deaths after age 55 from of lung, trachea, and bronchus by cumulative asbestos exposure to that age (Liddell *et al.*, 1997, Table 8). Standardized mortality ratios (SMRs) were calculated based on Quebec rates from 1950 onward, and Canadian, or a combination of Canadian and Quebec rates, for

earlier years. Table 2 shows the fit of the lung cancer model to these data. Although the models both with $\alpha = 1$ and α variable provided reasonably adequate fits to the data, the hypothesis $\alpha = 1$ can be rejected ($p = 0.007$). The model with α estimated yields a best estimate of KL of 0.00029 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00019, 0.00041). With $\alpha = 1$, the estimate was KL = 0.00041 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00032, 0.00051).

Smoking history was obtained in 1970 by a questionnaire administered to current workers at that time, and to proxies of those who had died after 1950. Although no analyses of lung cancer and asbestos exposure were presented for the 1992 followup (Liddell *et al.*, 1997) that controlled for smoking, such an analysis was conducted for the followup that continued through 1975 (McDonald et al., 1980a). Table 9 of McDonald *et al.* (1980a) contained data on lung cancer categorized jointly by cumulative exposure to asbestos and by smoking habit. Two models were fit to these data: the multiplicative model for relative risk

$$RR = \alpha(l + bd)(l+cx),$$

and the additive model

$$RR = \alpha(l + bd + cx),$$

where d is cumulative exposure to asbestos to age 45, x is number of cigarettes smoked per day, and α,b,c are parameters estimated from the data. The multiplicative model fit the data well, but the fit of the additive model was inadequate. This corroborates the multiplicative interaction between smoking and asbestos exposure in causing lung cancer (Hammond et al., 1979). The estimate of potency using the multiplicative model was 0.00051 $(\text{f-y/ml})^{-1}$, which was very close to that of 0.00045 $(\text{f-y/ml})^{-1}$ estimated from Table 5 of McDonald *et al.* (1980a), which did not utilize smoking data. This suggests that smoking is not strongly confounded with exposure in this cohort.

The best estimate of KL was assumed to be the MLE estimate with α variable. The uncertainty factors selected for this study were F1 = 2, F2 = 1.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

By 1993, 38 deaths from mesothelioma had occurred in this cohort (Liddell *et al.*, 1997). Through the courtesy of Dr. Corbett McDonald and Professor Douglass Liddell, the underlying mesothelioma data from this study were provided to us (Liddell, 2001, personal communication). These data contained the following information on each worker: the date of birth, asbestos exposure history, last date of followup, whether followup ended as a result of death from mesothelioma, location where they first worked, and whether they worked in more than one location.

Nine distinct locations for first employment were coded. Locations 5-9 referred to small

operations, some having very heterogeneous exposures, and were omitted from the analysis. Also, workers who worked at more than one location were omitted. After these exclusions, there remained 9244 workers who worked at Locations 1 - 4, and among whom 35 deaths from mesothelioma occurred. Location 1 (4195 men, 8 deaths from mesothelioma) was the mine and mill at the town of Asbestos. Location 2 (758 men, 5 deaths) was a factory at the town of Asbestos that, in addition to processing chrysotile, had also processed some crocidolite. Location 3 (4032 men, 20 deaths) comprised a major mining and milling company complex near Thedford Mines. Location 4 (259 men, 2 deaths) comprised a number of smaller mines and mills also in the vicinity of Thedford Mines. Because of the small number of workers at Location 4, the fact that both locations were near Thedford Mines, and the fact that the separate KM values obtained from Locations 3 and 4 were similar, data from these locations were combined. The remaining groups were analyzed separately, because of the crocidolite used at Location 2, and because of evidence of greater amounts of tremolite in the ore at Thedford Mines that at Asbestos (Liddell *et al.*, 1997).

The availability of the raw data from this study made it possible calculate KM from this study using an "exact" likelihood approach based on expression (3) that did not involve any grouping of data, or use of average values. For Location 1 (Asbestos mine and mill), KM = 0.013×10^{-8}, 90% CI: (0.0068×10^{-8}, 0.022×10^{-8}). For Location 2 (Asbestos factory), KM = 0.092×10^{-8}, 90% CI: (0.040×10^{-8}, 0.18×10^{-8}). For Locations 3 and 4, KM = 0.021×10^{-8}, 90% CI: (0.014×10^{-8}, 0.029×10^{-8}). The KM estimate from Location 1 (whose ore was reported to have a lower tremolite content) was about one-half that from Locations 3 and 4, although this difference was not significant ($p = 0.22$). The KM estimated from Location 2, the mill where substantial crocidolite was used, was four to seven times higher than the KL estimated from Location 1 and Locations 3 and 4.

For comparison purposes, KM were also calculated using grouped data and applying expression (4), since this is the method that must be used with most studies. For Location 1 (3&4) the KM estimate based on the "exact" analysis was 34% (25%) higher than that based upon grouped data. This suggests that reliance upon published data for calculating KM may introduce some significant errors in some cases. Such errors may be further compounded by the failure of some studies to report the needed data on levels and durations of exposure in different categories of time since first exposure.

The best estimate of KM for each location was assumed to be the MLE estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits, resulted in the likely range for KM shown in Table 1.

Italian Mine and Mill

Piolatto *et al.* (1990) conducted additional followup of workers at a chrysotile mine and

mill in Italy that was earlier studied by Rubino *et al.* (1979). The cohort consisted of 1058 workers with at least one year of employment between 1946 and 1987. Followup extended from 1946 through 1987, which is 12 more years of followup than in Rubino *et al.* (1979). Lung cancer mortality was compared to that of Italian men.

As described in Rubino *et al.* (1979), fiber levels were measured by PCM in 1969. In order to estimate earlier exposures, information on daily production, equipment changes, number of hours worked per day, etc. were used to create conditions at the plant during earlier years. PCM samples were obtained under these simulated conditions and combined with work histories to create individual exposure histories.

Piolatto *et al.* (1990) observed 22 lung cancers compared to 11 in the earlier study (Rubino *et al., 1979).* Lung cancer was neither significantly in excess nor significantly related to cumulative asbestos exposure. Piolatto *et al.* (1990, Table 1) presented observed and expected lung cancers (based on age- and calendar-year-specific rates for Italian men) categorized by cumulative exposure in f-y/ml. The lung cancer model with fixed α provided an adequate fit to these data (Table 3, $p = 0.42$) and allowing α to vary did not significantly improve the fit. The KL estimate with $\alpha = 1$ was 0.00035 $(\text{f-y/ml})^{-1}$, with 90% CI: (0,0.0015). With α allowed to vary the estimate was KL = 0.00051 $(\text{f-y/ml})^{-1}$ with 90% CI: (0,0.0057).

The best estimate of KL was assumed to be the MLE estimate with $\alpha = 1$. The uncertainty factors selected for this study were F1 = 2, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Two mesotheliomas were observed by Piolatto *et al.* (1990), compared to one found by Rubino *et al.* (1979). However, data were not presented in a form from which KM could be estimated.

Connecticut Friction Product Plant

McDonald et al. (1984) evaluated the mortality of workers employed in a Connecticut plant that manufactured asbestos friction products. The plant began operation in 1913 and used only chrysotile until 1957, when a little anthophyllite was used. Also, a small amount of crocidolite (about 400 pounds) was handled experimentally between 1964 and 1972. Brake linings and clutch facings were made beginning in the 1930s, and production of automatic transmission friction materials, friction disks and bands was begun in the 1940s.

The cohort was defined to include any man who had been employed at the plant for at least one month before 1959, omitting all that had worked at a nearby asbestos textile plant that closed in 1939. This cohort consisted of 3515 men, of whom 36% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only

begun past 20 years from first employment.

Information on dust levels from impinger measurements were available for the years 1930, 1935, 1936, and 1939. There was little other exposure information available until the 1970s. An industrial hygienist used these measurements and information on processes and jobs, environmental conditions and dust controls to estimate exposures by process and by period in units of mppcf. No conversion from mppcf to f/ml value was suggested by the authors, a conversion factor or between 1.4 and 10 is suggested by other studies. The most common value seems to be around 3 f/ml per mppcf, which has been observed in diverse environments such as mining and textile manufacture. This value was provisionally applied to this cohort, although this conversion has considerable uncertainty associated with it.

Total deaths and deaths from most individual causes investigated were elevated; these elevations were due primarily to increased deaths in the group working for less than one year. This pattern holds for lung cancer in particular; the SMR for lung cancer was highest (180) for persons exposed for less than one year. A similar pattern holds when the analysis was carried out by cumulative exposure (Table 4); the SMR in the lowest exposure category is higher than in any other category. The linear relative risk lung cancer model provided a poor fit ($p = 0.01$) to these data when the Connecticut rates were assumed to be appropriate for this cohort (fixing the parameter $\alpha = 1$); use of U.S. rates gave similar results. However, the fit was adequate ($p = 0.28$) if the background response is allowed to rise above that of Connecticut men (allowing the parameter α to vary). Although the reason for this increased response in persons that worked for a short period or have low exposures is not clear, the analysis in which the background response is allowed to vary appears to be the most appropriate. This analysis yields an estimate of $KL = 0.0$ $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0017). The analysis with $\alpha = 1$ yielded $KL = 0.0019$ $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0061).

The best estimate of KL was assumed to be the MLE estimate with $\alpha = 1$. The uncertainty factors selected for this study were F1 = 2, F2 = 3, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

McDonald et al. did not find any mesotheliomas in this cohort. It is useful to determine the range of mesothelioma risk that is consistent with this negative finding. Although McDonald et al. do not furnish data in the form needed for this calculation, these data can be approximated from McDonald et al.'s Table 1. In this table they list 511 deaths occurring after age 65. Assuming that the overall SMR of 108.5 held for persons over 65 years of age, the expected number of deaths is 511/1.085 = 471. The death rate in U.S. white males between 65 and 75 years of age is approximately 0.050 per year (from 1971 vital statistics). Therefore the number of person years observed in persons post 65 years of age is estimated as 471/0.050 = 9420.

A lower bound on the person-years of followup between ages 45 and 65 can be estimated by assuming that followup was complete for this age group. First we estimate the number of persons that would have had to have been in the cohort to experience the observed deaths. Assuming that x persons in the cohort are alive at age 45, we have the following estimates of the number entering each successive five-year age interval and the corresponding number of deaths (based on death rates in 1971 white males).

Age	Number Entering Interval	Number of Deaths in Interval	Person-Years in Interval
45-50	x	0.032x	4.9x
50-55	$x(1-0.00638)^5=0.97x$	0.052x	4.7x
55-60	$0.97x(1-0.01072)^5=0.92x$	0.076x	4.4x
60-65	$0.92x(1-0.01718)^5=0.84x$	0.11x	3.9x
65+	$0.84x(1-0.02681)^5=0.73x$		
TOTALS		0.27x	18.0x

Since there were 616 deaths in men between the ages of 45 and 65, the expected number of deaths is estimated as 616/1.085 = 567.7 expected deaths between ages of 45 and 60, the number of persons entering this age interval is estimated as x = 567.7/0.27 = 2100. The person-years is then estimated as (2100)(17.964) = 38000.

Using the average age of beginning work of 30.95 years (McDonald et al., 1984, Table 3) yields the data in Table 5. Moreover, the average duration of exposure in this cohort was 8.04 years and the average exposure level was 1.84 mppcf (McDonald et al, Table 3), which is equivalent to 1.84x3 = 5.52 fibers/ml. These data yields an estimate of KM = 0.0 and a 90% upper bound of KM = $1.2xlO^{-9}$.

The best estimate of KM was assumed to be zero. In addition to the uncertainty factors described earlier, an additional factor (F4M = 3) was applied to account for the crude method of analysis. When coupled with the statistical confidence limits, these resulted in the likely range for KM shown in Table 1.

New Orleans Asbestos-Cement Plants

Hughes *et al.* (1987) report on followup through 1981 of a cohort of Louisiana workers from two asbestos cement plants studied previously by Weill et al. (1979). Although chrysotile, amosite and crocidolite were used at these plants, a group of workers at one of the plants were only exposed to chrysotile. The cohort contained 6,931 workers, of whom 95% were traced, compared to a 75% success in tracing by Weill *et al.* (1979). This improved trace was the result both of greater access to Social Security

Administration records and greater availability of computerized secondary information sources (Dr. Hughes, personal communication).

Both of the plants have operated since the 1920s. Chrysotile was used predominantly in both plants. Some amosite was used in Plant 1 from the early 1940s until the late 1960s, constituting about 1% of some products, and crocidolite was used occasionally for approximately 10 years beginning in 1962. Plant 2 utilized only chrysotile, except that pipe production, which began in 1946 and was housed in a separate building, produced a final product that contained about 3% crocidolite. Since the total percentage of asbestos fiber in most asbestos cement products ranges from fifteen to 28 per cent, it is estimated that crocidolite constituted between ten and twenty per cent of the asbestos used to make cement pipe (Ontario Royal Commission, 1984). Workers from Plant 2 that did not work in pipe production were exposed only to chrysotile.

Estimates of airborne dust levels were made for each job by month and year from midget impinger measurements initiated in the early 1950s. Levels estimated from initial samples in the 1950s were also assumed to hold for all earlier periods because no major dust control measures had been introduced prior to that time. New exposure data from Plant 2 became become available after the earlier study (Weill *et al.*, 1979) was completed, and these, along with a complete review of all the exposure data, were used to revise the previous estimates of exposure. In Plant 1 the earlier and revised estimates were reasonably similar, but in Plant 2, the revised estimates tended to be about one-third of the previous estimates through the 1940s and about one-half the previous estimates thereafter. Based on 102 side-by-side measurements by midget impinger and PCM in various areas of one of the plants, Hammond et al. (1979) estimated an overall conversion factor of 1.4 fibers/ml per mppcf. There were substantial variations in this factor among different areas of the plant.

The principal cohort studied consisted of all workers who, according to company records, were employed for at least one month prior to 1970, had a valid Social Security number, and were first employed in 1942 or later (Plant 1) or in 1937 or later (Plant 2). Mortality experience was compared with that expected based on Louisiana rates.

Hughes et al. found no significant difference between the dose responses for lung cancer in Plant 2 among workers exposed to chrysotile only and those who were also exposed to crocidolite in pipe production. A single lung cancer dose response model adequately describes the lung cancer data from Plants 1 and 2 combined ($p >= 0.42$, Table 6). The fit of this model is good when Louisiana men are assumed to be an appropriate control group (fixing the parameter $\alpha = 1$). This fit provides an estimate of $KL = 0.004$ (fiber-y/ml)$^{-1}$, 90% CI: (0.001, 0.007) With α allowed to vary, the estimate is 0.003 (fiber-y/ml)$^{-1}$, 90% CI: (0, 0.007).

The best estimate of KL was assumed to be the MLE estimate with $\alpha = 1$. The uncertainty factors selected for this study were F1 = 2, F2 = 1.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Six mesotheliomas were identified in the primary cohort studied by Hughes et al., two in Plant 1 and four in Plant 2. Four other mesotheliomas are known to have occurred, one among those initially employed in Plant 2 before 1937 and three among Plant 2 workers shortly after followup ended in 1981. A case control analysis conducted among Plant 2 workers found a relationship between mesothelioma risk and length of employment and proportion of time spent in the pipe area after controlling for length of exposure, which is consistent with a greater risk of mesothelioma from crocidolite exposure.

Data were not presented in the paper in the form required for estimating KM. However, Hughes and Weill (1986) present estimates of mesotheliomas potency from several data sets, including the cohort studied in Hughes et al. and containing six mesotheliomas, but using a model slightly different from the 1986 EPA model (3). Estimating KM by multiplying the potency estimated by Hughes and Weill model by the ratio of the potency values estimated for another study using the 1986 EPA model and the Hughes-Weill model yielded the following estimates of KM for the Hughes et al. data: 0.25×10^{-8} (Selikoff et al., 1979); 0.21×10^{-8} (Dement et al., 1983b); 0.27×10^{-8} (Seidman, et al., 1979); and 0.43×10^{-8} (Finkelstein, 1983). Based on these calculations, KM = 0.30×10^{-8} seems to be a reasonable estimate for the Hughes et al. cohort.

It would be worthwhile to estimate mesothelioma risk using additional followup that included the three cases that occurred shortly after followup ended. However, such an estimate should be no larger than about KM = 0.45×10^{-8}. This is because, since there were six mesotheliomas in the cohort studied by Hughes et al., even if the additional person years of followup post 1981 is not taken into account, the three additional mesotheliomas would increase the estimate of KM by only about 50%.

Hughes et al.'s finding of an association with crocidolite exposure implies that a smaller KM would correspond to the chrysotile-only exposed group in Plant 2. Although Hughes et al. didn't furnish the data needed for precise estimation of KM from this cohort, it is possible to make some reasonable approximations to this KM. Since none of the six mesotheliomas occurred among workers exposed only to chrysotile, KM = 0 would be the point estimate derived from the data used by Hughes et al.

However, one mesothelioma was discovered in a person whose employment began in 1927 and thus was not eligible for inclusion in the cohort. This person was employed continuously for 43 years in the shingle production area, where only chrysotile was used. In an attempt to compute an alternative KM using this one case, it was noted that the duration of observation of the Hughes et al. cohort was roughly equivalent to that of

the Dement et al. (1983b) cohort. If the person-years from this cohort, categorized by years since first exposure, are adjusted by the ratio of the sizes of Dement et al. and the Hughes et al. non-crocidolite-exposed cohort from Plant 2, one mesothelioma is assumed to occur (in 30+ years from first exposure category) and the average duration of exposure (2.5 years) and fiber level (11.2 fibers/ml) appropriate for the Hughes et al. cohort are applied to these data, a KM = 0.2×10^{-8} is obtained.

The best estimate of KM was assumed to be 0.2×10^{-8} for workers exposed only to chrysotile and 0.3×10^{-8} for workers exposed to both chrysotile and amphibole. Since no confidence interval was available for these values, additional uncertainty factors were included (F4M = 5, for chrysotile exposures and 2.5 for mixed exposures), which, when coupled with the other uncertainty factors discussed earlier, resulted in the likely range for KM shown in Table 1.

South Carolina Textile Factory

Dement and coworkers (Dement *et al.*, 1994; Dement and Brown, 1998) conducted a retrospective cohort study of employees of a chrysotile textile plant in South Carolina. In an earlier study of this plant (Dement *et al.* 1982, 1983a, 1983b), the cohort was defined as all white male workers who worked for one or more months between 1940 and 1965, and followup was through 1975. Dement *et al.* (1994) expanded the cohort to include black male and white female workers who met the entrance requirements, and extended followup through 1990, an additional 15 years. This expanded cohort included 1247 white males (2.8% lost to followup), 1229 white females (22.8% lost to followup) and 546 black males (7.8% lost to followup). A total of 1259 deaths were identified, and a death certificate was located for all but 79 (6.2%) of the deaths.

Based on data from 5,952 air samples taken at the plant between 1930 and 1975, linear statistical models were used to reconstruct exposure levels, while taking into account textile processes, dust control methods, and job assignments (Dement *et al.*, 1983a). For each worker, time spent in each job was multiplied by the estimated exposure level for that job to estimate cumulative exposure (f/ml-days). Based on regression analyses applied to 120 side-by-side particle and fiber counts, Dement (1980) estimated a f/ml to mppcf ratio of 2.9, 95% CI: (2.4, 3.5). Also, between 1968 and 1971 both impinger and PCM samples were collected (a total of 986 samples). Based upon a regression analysis of these data, Dement (1980) determined that a common conversion factor could be used for jobs except fiber preparation. For fiber preparation, a conversion factor of 7.8 was found, 95% CI: (4.7-9.1). For all other operations, a value of 2.5, 95% CI: (2.1-3.0) was calculated. Based on this information, Dement *et al.* (1983a) concluded that a conversion factor of 3 was appropriate for all operations except preparation, for which a factor of 8 was adopted.

The underlying data for this cohort were obtained from the National Institute for Safety and Health (NIOSH). These data consisted of a work history file and a file with exposure levels by job category and time period. The work history file contained codes for race, sex, month and year of birth, vital status, month and year of death, and the department, operation, start date, and stop date for each job worked. The exposure level file contained the exposure start and stop dates and the exposure level (fiber/ml) by the plant code, the department code, and the operation code.

The cohort was defined as the white and black males and the white females who met the employment requirements described above. This cohort included 1244 white males (1.5% lost to followup), 550 black males (7.5% lost to followup), and 1228 white females (22.1% lost to followup).

Table 7 shows observed and expected deaths for lung cancer among white males, black males and white females, categorized by cumulative exposure. This table shows an excess of lung cancers that exhibited a dose response relationship. U.S. rates were used for calculating expected deaths, whereas South Carolina lung cancer rates are higher for white men but slightly lower for white women and black men. Whereas twelve categories of cumulative exposure were used for fitting the model, these were been combined into seven categories for display in Table 7. The model with $\alpha = 1$ and α variable fit the data adequately ($p \geq 0.2$), and the hypothesis that $\alpha = 1$ cannot be rejected ($p = 0.21$). The estimate of KL with $\alpha = 1$ was 0.028 $(\text{f-y/ml})^{-1}$, 90% CI: (0.021, 0.037), and the estimate with α variable was KL = 0.021 $(\text{f-y/ml})^{-1}$, 90% CI: (0.012, 0.034). An analysis applied to white men alone gave somewhat higher estimates (KL = 0.040 $(\text{f-y/ml})^{-1}$ with $\alpha = 1$, and KL = 0.026 $(\text{f-y/ml})^{-1}$ with α variable).

Because the chi-square goodness of fit test could not reject the model with $\alpha = 1$ even though $\alpha = 1$ could be rejected the best estimate of KL was assumed to be the geometric mean of the MLE estimates with $\alpha = 1$ and α variable. The uncertainty factors selected for this study were F1 = 1.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Two deaths were certified as due to mesothelioma on the death certificates. In addition, Dement *et al.* (1994) considered four other deaths as likely due to mesothelioma. The availability of the raw data from this study made it possible calculate KM from this study using an "exact" likelihood approach based on expression (3) that did not involve any grouping of data, or use of average values. Using the six confirmed and suspected mesotheliomas, KM = 0.43×10^{-8}, 90% CI: (0.20×10^{-8}, 0.79×10^{-8}). Using the two confirmed mesotheliomas, KM = 0.14×10^{-8}, 90% CI: (0.034×10^{-8}, 0.38×10^{-8}).

For comparison purposes, KM were also calculated using grouped data and applying expression (4), since this is the method that must be used with most studies. The data

were divided into 10 categories by the tabulated values of expression (4). The KM estimate based on the "exact" analysis was 2% greater than that based upon grouped data.

The best estimate of KM was assumed to be the geometric mean of the MLE estimates computed using either confirmed or both confirmed and suspected mesotheliomas (0.25×10^{-8}). The statistical lower bound used for this estimate was the one based on confirmed cases and the upper bound used was the one based on confirmed and suspected cases. The uncertainty factors described earlier, when coupled with these statistical confidence limits, resulted in the likely range for KM shown in Table 1.

McDonald et al. (1983a) conducted a cohort mortality study in the same South Carolina textile plant that was studied by Dement et al. (1994). Their cohort consisted of all men employed for at least one month before 1959 and for whom a valid social security record existed. This cohort consisted of 2410 men, of whom 36% had died by the end of followup (December 31, 1977). Followup of each worker was begun past 20 years from first employment.

McDonald et al. had available the same exposure measurements as Dement et al. (1983b) and used these to estimate cumulative exposures for each man in mppcf-y. In their review of the environmental measurements in which both dust and fiber concentrations were assessed, they found a particle to fiber conversion range of from 1.3 to 10.0 with an average of about 6 fibers/ml per mppcf. This value, which is intermediate between the values of 3 and 8 found by Dement et al. for different areas of the same plant, will be used in the calculations involving the McDonald et al. (1983a) study.

McDonald et al. describe two practices at the plant that entailed very high exposures and which were not reflected in either their's or Dement et al.'s estimates: cleaning of burlap bags used in the air filtration system by beating them with buggy whips during the years 1937-53, and the mixing of fibers, which was carried out between 1945 and 1964 by men with pitch forks and no dust suppression equipment.

A strong dose response for lung cancer was observed (Table 8), which parallels the results of Dement et al. (1994). Unlike Dement et al., McDonald et al. used South Carolina men as the control group rather than U.S. men. Use of this control group provided an adequate description of the data and lung cancer potency values estimated both with $\alpha = 1$ and allowing α to vary provided excellent descriptions of the data ($p >= 0.88$) and the hypothesis $\alpha = 1$ could not be rejected ($p = 0.36$). Assuming $\alpha = 1$ resulted in KL = 0.012 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0075, 0.016), and when α was allowed to vary, KL = 0.010 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0044, 0.025). These results are reasonably consistent with the potency estimated from Dement et al. (1994), and the differences can be largely accounted for by the different assumptions regarding the fiber/particle

ratio.

The best estimate of KL was assumed to be the MLE estimate with $\alpha = 1$. The uncertainty factors selected for this study were F1 = 2, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

McDonald et al. found one case of mesothelioma in this cohort, apparently the same one discovered by Dement et al. (1983b): a man born in 1904 who died in 1967 and worked at the plant for over 30 years. Since this study was conducted exactly as McDonald et al. (1984), the same method used there to reconstruct person-years by years from first exposure can be applied to this cohort as well. The reconstructed data are listed in Table 9. The estimated potency MLE is KM = 0.088 $x10^{-8}$, with a 90% confidence interval of (0.0093xIO^{-8}, 0.32xIO^{-8}).

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits and an additional factor to account for the reconstructed person years (F4M = 3) resulted in the likely range for KM shown in Table 1.

Predominant Crocidolite Exposure

Wittenoom, Australia Mine and Mill

de Klerk *et al.*, 1994 followed a cohort of 6904 men and women employed at a crocidolite mine and mill in Wittenoom, Australia. This cohort was followed through 1999 and the raw data were obtained through the courtesy of Dr. de Klerk. The data consisted of a record number, date of birth, sex, employment start date, total days of employment, average exposure level (f/cc), cumulative exposure (f-Yr/cc), date of last contact, ICD code for cause of death, indicator variable for mesothelioma death, and date of death if applicable.

A number of subjects from the full cohort were removed from the analysis reported herein: 412 because the sex was not designated as male; One because the date of last contact was missing; 1275 subjects because the followup period was less than five years; 41 because the number of days worked was 0 or missing. After these subjects were removed, the cohort consisted of 5173 men who were employed at Wittenoom Gorge between 1943 and 1966.

The concentrations of fibers greater than 5 mm in length as measured by PCM were measured at various work sites in a survey conducted in 1966. Job category data were obtained from employment records and supplemented by records from the Perth Chest Clinic and the Western Australian Mineworkers Relief Fund. The concentration measurements and job category information were used to estimate the exposure level

for each subject in the cohort (DeKlerk *et al.*, 1989). The exposure levels were high with a median of 17.8 (fiber/ml). The durations of employment were low with a median of 128 days.

There were 251 lung cancer deaths in the cohort. Table 10 shows the observed, expected, and predicted lung cancer deaths among the males categorized by cumulative exposure (fiber-year/ml). The number of expected lung cancer deaths are based on Australian lung cancer mortality rates. With no allowance for difference between the background lung cancer death rates among Australia and the members of this cohort (a = 1), the fit of the model is poor ($p < 0.01$). Allowing for difference in the background lung cancer death rates (a variable), the model provides a reasonably good fit to the data ($p = 0.10$) and estimates KL = 0.0047 $(\text{fiber-year/ml})^{-1}$, 90% CI: (0.0017, 0.0087). The hypothesis a = 1 can be rejected with high confidence ($p < 0.01$).

The best estimate of KL was assumed to be the MLE estimate with α variable. The uncertainty factors selected for this study were F1 = 2, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

There were 165 mesotheliomas in the cohort. The availability of the raw data from this study made it possible calculate KM from this study using an "exact" likelihood approach based on expression (3) that did not involve any grouping of data, or use of average values. With this approach, KM = 7.95×10^{-8}, 90% CI: (6.97×10^{-8}, 9.01×10^{-8}).

For comparison purposes, KM were also calculated using grouped data and applying expression (4), since this is the method that must be used with most studies. The KM estimate based on the "exact" analysis was 12% lower than the estimate based upon grouped data.

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits, resulted in the likely range for KM shown in Table 1.

Predominant Amosite Exposure

Patterson, N.J. Insulation Factory

Seidman *et al.* (1986) studied a cohort of 820 men (mostly white) who worked at an amosite asbestos factory that operated in Patterson, New Jersey from 1941 through 1954. The men began work between 1941 and 1945 and followup was through 1982. The followup of a worker began five years following the beginning of employment. Workers who had prior asbestos exposure were not included in the cohort, and followup was stopped when a worker was known to have begun asbestos work elsewhere (6 men). Exposures were generally brief, as 76% were exposed for two years or less,

although a few were exposed for as long as 10 years.

No asbestos exposure measurements are available for this plant. Estimates of exposures in particular jobs were made based on air measurements made between 1967 and 1970 at plants in Tyler, Texas and Port Allegheny, Pennsylvania that were operated by the same company and made the same products using some of the same machinery as the Patterson facility. The estimated median exposure level was 50 f/ml. Amosite was the only type of asbestos used at the plant.

Seidman *et al.* cross-categorized lung cancer deaths by cumulative exposure (eight categories of f-y/ml) and length of time worked (seven categories, Seidman *et al.*, 1986, Table XXXIV). Although this table apparently was created by categorizing workers by their final cumulative exposure (rather than categorizing person-years of followup by the cumulative exposure to that point in time, which is more appropriate for calculating a KL), because exposures were brief this likely made little difference. Expected number of lung cancer deaths were based on age- and year-specific rates for New Jersey white males.

Table 11 shows the results of applying the lung cancer model to these data, after collapsing the table by summing over length of time worked. Results were highly dependent upon whether or not the background lung cancer mortality rate was assumed to be equal to that predicted by the comparison population of New Jersey white males (equivalent to $\alpha = 1$). The test for departure from the null hypothesis, $\alpha=1$, was highly significant, and the maximum likelihood estimate was $\alpha = 3.3$. Similarly, the model gave a poor overall fit to the data with $\alpha= 1$ ($p < 0.01$), but the fit was quite good when α was allowed to vary ($p = 0.90$). The estimated potency parameter, KL, also was highly dependent upon the assumption regarding the parameter, α. The estimate of KL was 0.062 $(\text{f-y/ml})^{-1}$, 90% CI: (0.050, 0.076), when α was fixed at $\alpha = 1$, and 0.011 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0058, 0.019), when α was allowed to vary, a six-fold difference. The lung cancer model was also fit to the data cross-classified by both cumulative exposure and length of time worked, allowing α to assume a different value in each category of time worked. Although the estimated values of α tended to increase with increasing duration of exposure, allowing different values of α did not significantly improve the fit ($p = 0.64$).

The reason for this behavior is not clear. There is no indication that workers with shorter durations experienced disproportionately high mortality, since, as noted above, α tended to increase with increasing duration of exposure. Although it is possible that cumulative exposure is not the appropriate exposure metric, it is difficult to envision what metric would predict this response, so long as a linear model is assumed. It is also possible that a linear model for relative risk is not correct and a supralinear model is more appropriate, or that the increased risk is not proportional to the background risk, as assumed by this simple relative risk model. Finally, it is possible that the

background rate in this population is significantly greater than that in the comparison population, although it seems unlikely that it could be three times greater as suggested by the model.

It is not clear what is the best estimate of KL in this case. If α is fixed at $\alpha = 1$, the model underpredicts risk at low exposures and overpredicts at high exposures. On the other hand if α is estimated, the resulting estimate of 3.3 seems unrealistically high. Provisionally, 0.026 $(\text{f-y/ml})^{-1}$, the geometric mean of the two MLE estimates with $\alpha = 1$ and α estimated will be used as the best estimate of KL for this cohort. The uncertainty factors selected for this study were F1 = 3.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Seidman *et al.* (1986) discovered 17 deaths from mesothelioma in this population. Table III of Seidman *et al.* categorized mesothelioma deaths and person-years of observation by years since onset of work. In order to apply the 1986 EPA mesothelioma model it is necessary to have estimates of the duration of exposure and level of exposure for each category. Using the categorization of the members of the cohort by duration of work in Table XXIII of Seidman *et al.*, it was estimated that the mean duration of work was 1.5 years. Using data from Seidman *et al.*, Table XIV, an average cumulative exposure was for each category of time from onset of exposure by weighting exposures according to the expected total number of deaths. These averages were divided by 1.5 years to obtain the average fiber concentrations in Table 12. The estimated exposure levels decrease with time since onset, which is consistent with higher mortality among more heavily exposed workers.

The 1986 mesothelioma model provided an adequate fit to these data ($p = 0.35$), although it over-predicted somewhat the number of cases in the highest latency category (> 35 years). The estimate of KM was 3.9×10^{-8}, 90% CI: $(2.6 \times 10^{-8}, 5.7 \times 10^{-8})$.

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits, resulted in the likely range for KM shown in Table 1.

Tyler, Texas Insulation Factory

Levin *et al.* (1998) studied the mortality experience of 1121 men who formerly worked at a plant in Tyler, Texas that manufactured asbestos pipe insulation. The plant operated from 1954 through February, 1972. The plant used the same raw materials and some of the same equipment that was used in the Patterson, New Jersey plant that was studied by Seidman *et al.* (1986). The asbestos used was amosite from the Transvaal region of South Africa. The insulation was manufactured from a mixture that contained 90% amosite asbestos.

Environmental surveys were conducted at the plant in 1967, 1970 and 1971, with average fiber concentrations ranging from 15.9 through 91.4 f/ml. An average exposure of 45 f/ml is assumed for this plant, which is near the middle of this range obtained in the three surveys. It is also consistent with average levels assumed for the Patterson, New Jersey plant, which operated under very similar conditions.

The cohort consisted of 744 whites, 305 non-white (mostly black), and 72 with missing race (assumed to be white, based on hiring practices at that time). For the entire cohort, the median age of first employment was 25 years, and the mean duration of employment was 12.7 months (range of one day to 17.3 years). Followup was through 1993. Death certificates were obtained for 304 of the 315 men known to be dead. In the mortality analysis only white men were evaluated and followup started ten years after first employment. After additional exclusions of men with missing birth dates or missing employment information, the cohort analyzed in the mortality analysis consisted of 753 former workers, among whom 222 deaths were recorded. These deaths were compared with those expected based on age, race and sex-specific U.S. rates.

There was an excess of deaths from respiratory cancer (SMR = 277, based on 36 deaths, not including four deaths from mesothelioma). Table 13 contains observed and expected numbers of deaths from respiratory cancer, categorized by duration of exposure. Cumulative exposure in f-y/ml was estimated by multiplying the duration of exposure times the assumed average fiber level of 45 f/ml. There was an excess of lung cancer deaths in the lowest exposure group (23 observed, 8.9 expected), and consequently the model with $\alpha = 1$ did not fit these data ($p < 0.01$), and the hypothesis $\alpha = 1$ could be rejected ($p < 0.01$). The KL with α variable was KL = 0.0013, 90% CI: (0, 0.006). With $\alpha = 1$, KL = 0.013 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0055, 0.022).

The best estimate of KL was assumed to be the MLE estimate with α variable. The uncertainty factors selected for this study were F1 = 3, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Four mesotheliomas were reported in this study. However, the data are not presented in a form that would permit application of the EPA 1986 mesothelioma model.

<u>Predominant Tremolite-Actinolite Exposure</u>

Libby, Montana Vermiculite Mine

Amandus and Wheeler (1987) conducted a retrospective cohort study of 575 men who were exposed to tremolite-actinolite while working at a vermiculite mine and mill in Libby, Montana. A dry mill began operation in 1935 and a wet mill began operating in the same building as the dry mill in 1950 (Amandus *et al.*, 1987).

A total of 376 impinger samples were available that had been collected during 1950-1969, although only 40 of these were collected prior to 1965. In addition 4118 PCM samples were available from the period 1967-1982. Exposure estimates for years later than 1968 were based on historical measures of fiber concentrations (f/ml), and those for earlier years were based on concentrations measured by midget impinger (mppcf) and converted to f/ml assuming a conversion ratio of 4 f/ml per mppcf. This conversion factor was derived from 336 impinger samples collected during 1965-1969 and 81 filter samples collected during 1967-1971. Individual cumulative fiber exposure estimates (f-y/ml) were computed from job-specific exposure estimates and work histories (Amandus *et al.*, 1987).

The cohort consisted of all men hired prior to 1970 and employed for at least one year in either the mine or the mill. Followup was through December 31, 1981. The vital statuses of 569 of the men (99%) were determined and death certificates were obtained for 159 of the 161 who were deceased.

Smoking information was available for 161 men employed between 1975 and 1982 and with at least five years of tenure. The proportion of these workers who smoked (current or former) was 84% compared to 67% among U.S. white males during the same time period.
A total of 20 deaths from lung cancer were observed (9 expected, SMR = 223.2, using U.S. white males as the comparison population). Table 14 (based on Amandus and Wheeler, 1987, Table II) shows that the excess occurred mainly in workers whose cumulative exposure exceeded 400 f-y/ml (10 observed, 1.7 expected). The 1986 EPA lung cancer model fit these data adequately ($p \geq 0.25$) both with $\alpha = 1$ and α variable, and the hypothesis $\alpha = 1$ could not be rejected ($p = 0.4$). With $\alpha = 1$, KL was estimated as 0.0061 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0029, 0.010), and with α variable, KL = 0.0051 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0011, 0.020).

The best estimate of KL was assumed to be the MLE estimate with $\alpha = 1$. The uncertainty factors selected for this study were F1 = 2.5, F2 = 1.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Amandus and Wheeler (1987) observed 2 deaths from mesothelioma in this cohort. However, information on these cases was not sufficient to permit application of the 1986 EPA mesothelioma model.

McDonald *et al.* (1986) also conducted a cohort study of workers at the Libby, Montana vermiculite mine and mill. Their cohort was composed of 406 workers employed prior to 1963 for at least one year. Followup was until July 1983. Vital status was determined for all but one man and death certificates were obtained for 163 of the 165 men who had died. Cumulative exposures (f-y/ml) were estimated for each worker

using work histories based on 42 job categories, and 1363 environmental measurements, including samples analyzed by PCM (f/ml) and by midget impinger (mppcf).

A total of 23 deaths from lung cancer were observed (SMR = 303, based on Montana rates). Table 15 shows these deaths categorized by cumulative exposure (based on Table 4 of McDonald *et al.*, 1986). Both the models with $\alpha = 1$ and α variable fit these data adequately ($p \geq 0.16$) although the hypothesis $\alpha = 1$ could almost be rejected ($p = 0.057$). The estimate of KL with $\alpha = 1$ was 0.011, $(\text{f-y/ml})^{-1}$, 90% CI: (0.0055, 0.017), and with α variable, KL = 0.0039 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00067, 0.012).

Since the test of the hypothesis $\alpha = 1$ was close to significance, KL was assumed to be the geometric means of the MLE estimates from $\alpha = 1$ and α variable. KL estimate with MLE estimate with α variable. The uncertainty factors selected for this study were F1 = 2.5, F2 = 1.5, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

McDonald *et al.* (1986) observed 2 deaths from mesothelioma. However, information on these cases was not sufficient to permit application of the 1986 EPA mesothelioma model.

Exposure to Mixed Fiber Types

British Friction Products Factory

Berry and Newhouse (1983) conducted a mortality study of 13,460 workers in a factory in Britain that manufactured brake blocks, brake and clutch linings, and other friction materials. Only chrysotile was used at the plant except for two relatively short periods before 1945 when crocidolite was used in the production of railway blocks.

The cohort studied consisted of all men or women employed at the plant between 1941 and 1977. Follow-up was to the end of 1979 and the mortality experience was examined after 10 years from first exposure. Airborne dust measurements were only available from 1967 onward and these were made using the PCM method. Fiber concentrations in earlier years were estimated by reproducing earlier working conditions using knowledge of when processes were changed and exhaust ventilation introduced.

Deaths from all causes were less than expected both prior to ten years from first employment (185 observed versus 195.7 expected) and afterward (432 observed versus 450.8 expected). There was no indication of an effect of employment at the plant upon lung cancer; there were 51 lung cancers more than ten years from first employment compared to 47.4 expected. A significant deficit of gastrointestinal

cancers was observed after ten years from first employment (25 observed versus 35.8 expected, p = 0. 04).

A linear dose response model relating cumulative exposure and lung cancer was fit to case-control data presented by Berry and Newhouse. The resulting KL was 0.00058 $(f\text{-}y/ml)^{-1}$ and the 95% upper limit was 0.0080 $(f\text{-}y/ml)^{-1}$. This estimate was used as the best estimate of KL, and and the lower confidence bound was assumed to be zero. The uncertainty factors selected for this study were F1 = 3, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

A case control study on mesothelioma deaths showed that eight of the eleven cases had been exposed to crocidolite and another possibly had intermittent exposure to crocidolite. The other two had been employed mostly outside the factory and possibly had other occupational exposures to asbestos. The case control analysis showed that the distribution of cases and controls in respect to exposure to crocidolite was quite unlikely assuming no association with crocidolite. This indicates that some, and possibly all, of the eight mesotheliomas with crocidolite exposure were related to this exposure. The data were not presented in a form that permitted a quantitative estimate of mesothelioma risk.

Ontario Asbestos-Cement Plant

Finkelstein (1984) studied mortality among a group of 535 exposed and 205 unexposed employees of an Ontario asbestos-cement factory who had been hired before 1960 and who had been employed for at least one year. This cohort contained the cohort studied by Finkelstein (1983) and which required at least nine years of employment for membership. Follow-up continued until 1977 or 1981.

The plant produced asbestos cement pipe from 1948, asbestos cement board from 1955-1970, and manufacture of asbestos insulation materials was added in 1960. Both chrysotile and crocidolite were used in each batch processed in the pipe process, but only chrysotile was used in the cement board operation. Crocidolite constituted approximately 20% of the asbestos used in the pipe process (Ontario Royal Commission, 1984).

Fiber concentrations in various work areas and for various epochs were estimated from membrane filter samples taken after 1969, impinger measurements taken during 1949, 1954, 1956, 1957 and semiannually during the 1960s, and information on changes in dust control methods. Finkelstein judged that the resulting exposure estimates were "probably accurate to within a factor of three or five." Exposures of maintenance workers were not estimated, and the exposure response analysis consequently involved only the unexposed workers (N = 205) and the production workers (N = 428).

Only 21 deaths from lung cancer were observed among production workers. Based on these deaths, Finkelstein compared age-standardized lung cancer mortality rates in production workers after a 20-year latency, categorized into five groups according to their cumulative exposure through 18 years from date of first employment (Finkelstein, 1984, Table 7). Mortality rates were standardized with respect to age and latency using the man-years distribution in the cohort as a whole as the standard. Using similarly standardized mortality rates in Ontario males as the comparison population, lung cancer rates were elevated in all five categories, and Finkelstein found a significant exposure-response trend. However, the trend was not monotone, as rates increased up to the middle exposure category and decreased thereafter (Table 16).

These data may be put into a form roughly equivalent to the more conventional age-adjusted comparison of observed and expected lung cancer deaths by dividing the rates in the exposed group by that of Ontario men. (The rate for unexposed workers was not used because it was based on only 3 deaths.) The results of this are shown in Table 16, which also shows the results of fitting the 1986 EPA lung cancer model both assuming the Ontario rates were appropriate for this cohort (fixing the parameter $\alpha = 1$) and not making this assumption (allowing the parameter α to vary). Neither approach provided an adequate fit to these data ($p \leq 0.05$) and the hypothesis $\alpha = 1$ was rejected ($p = 0.03$). The maximum likelihood estimate of α was 4.26, which seems too large to be due to differences in smoking habits. The KL estimate with $\alpha = 1$ was 0.048 $[\text{f-y/ml}]^{-1}$, 90% CI: (0.028,0.074). With α allowed to vary the estimate was KL = 0.0029 $[\text{f-y/ml}]^{-1}$, 90% CI: (0,0.037). The fact that the lower limit was zero indicates that the dose-response trend was not significant when the background was allowed to vary.

Because the hypothesis $\alpha = 1$ was rejected but neither $\alpha = 1$ nor α estimated gave an adequate fit to these data, the best estimate of KL was assumed to be the geometric means of the MLE estimates from $\alpha = 1$ and α variable. The uncertainty factors selected for this study were F1 = 4, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Based on a "best evidence" classification of cause of death, Finkelstein identified 17 deaths from mesothelioma among production workers. Table 3 of Finkelstein (1984) gives these mesotheliomas categorized by years since first exposure. This table also provides the mortality rate, from which can be calculated the person-years of observation. Finkelstein states that the average cumulative exposure for production workers was about 60 f-y/ml, but does not provide information for determining duration and level of exposure separately. CHAP (1983) used an average exposure of 9 f/ml for a subcohort of production workers, although they provided no support for this assumption. If this value is assumed to be appropriate for the expanded cohort, the average duration is estimated as about 60/9 = 6.7 years. However these values are uncertain. Table 17 presents the result of applying the 1986 EPA mesothelioma model to the Finkelstein (1984) data based on these assumptions. The mesothelioma model

describes these data adequately (p = 0.26) and provides an estimate of KM = $18x10^{-8}$, 90% CI: ($13x10^{-8}$, $24x10^{-8}$).

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits and an additional factor to account for the estimated exposure level (F4M = 2), resulted in the likely range for KM shown in Table 1.

Swedish Asbestos-Cement Plant

Albin *et al.* (1990) studied workers at a Swedish plant that operated from 1907 to 1978 and produced various asbestos cement products, including sheets, shingles, and ventilation pipes. The asbestos handled was mainly chrysotile (> 95%). Crocidolite was used before 1966 but never exceeded 3-4% of the total asbestos. Amosite was used for a few years in the 1950s but never exceeded 18% of the total asbestos used. Fiber length classes were the commercial grades 3-7, and all asbestos was milled prior to incorporation into products.

Impinger and gravimetric dust measurements were available for 1956-1969, and PCM measurements after 1969. These data, along with information on production and dust control, were used to estimate exposures for different jobs and periods of time.

The cohort contained 2898 men and was defined as all male employees who worked for at least three months between 1907 and 1977. A reference cohort was composed of 1233 men who worked in other industries in the region and who were not known to have worked with asbestos. Vital status of both groups was determined through 1986. Followup of both began after 20 years from first employment.

Excluding mesothelioma, other respiratory cancers were not significantly increased. Albin *et al.* present relative risks of these respiratory cancers and corresponding 95% confidence intervals for three categories of cumulative exposure (Table 18), based on Poisson regression with control for age and calendar year. In order to obtain crude estimates of the range of KL that are consistent with these data, the 1986 EPA lung cancer relative risk model was fit, assuming that the Ln (RR) were normally distributed with fixed variances computed from the reported confidence intervals for the RR. Although elevated, the RR did not exhibit a dose response, and the hypothesis $\alpha = 1$ was rejected (p = 0.02). In this analysis KL was not significantly different from zero, regardless of whether α was fixed at 1.0 or estimated. With $\alpha = 1$ the estimate of KL was 0.019 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.065), and KL = 0.00067 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.036) with α estimated.

Because the hypothesis $\alpha = 1$ was rejected, the best estimate of KL was assumed to

be the geometric means of the MLE estimates from $\alpha = 1$ and α variable. The uncertainty factors selected for this study were F1 = 4, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Thirteen mesotheliomas were identified among exposed workers and one in the referent population, and a significant dose response was observed with increasing cumulative exposure. Unfortunately, the mesothelioma data were not presented in a format that would permit application of the 1986 EPA mesothelioma model.

Belgium Asbestos-Cement Plant

Lacquet et al. (1980) conducted a roentgenologic, asbestosis, and mortality study in a Belgium asbestos cement factory employing about 2400 employees that annually processed about 39,000 tons of asbestos, of which 90% was chrysotile, 8% crocidolite, and 2% amosite. The mortality study considered male workers who worked in the factory for at least 12 months during the 15-year period 1963-1977. Apparently no minimal latency was required before followup began.

Fiber counts were available for the years 1970-1976; fiber levels were estimated for as far back as 1928, but these estimates were considered to be "only good guesses at best." Individual exposures were estimated in fiber-years from work histories and estimated yearly concentrations in four work areas.

The incidence of respiratory cancer was very close to that which was expected in a Belgium population of matched age and sex (Table 19). The models with $\alpha = 1$ ($p = 0.51$) and α variable ($p = 0.39$) gave similar results and the hypothesis $\alpha = 1$ was not rejected ($p = 0.34$). With $\alpha = 1$, the estimate of KL was 0.0 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0010). With α estimated, KL = 6.8×10^{-5} $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0021).

The estimate of KL with $\alpha = 1$ was assumed to be the best estimate. The uncertainty factors selected for this study were F1 = 4, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

One death was due to pleural mesothelioma. Unfortunately, the data were not presented in a way that allowed the estimation of KM.

Retirees from U.S. Asbestos Products Company

Enterline *et al.* (1986) extended followup through 1980 for a cohort of U.S. retirees from a large asbestos products company that had been the subject of an earlier report (Henderson and Enterline, 1979). Products manufactured by the company included

textiles, cement shingles, sheets, insulation and cement pipe. Exposure was predominately to chrysotile in most operations, although amosite predominated in insulation production, and crocidolite in manufacture of cement pipe. Each worker's exposure was estimated from dust measurements in mppcf obtained from environmental surveys that started in the mid-1950's and were extrapolated back in time by the company industrial hygienist. No data are provided for conversion from mppcf to PCM in f/ml. Given the wide range of products manufactured, this conversion likely varied according to operation. Conversions calculated in different environments have ranged from 1.4 to 10, the most common value being around 3 f/ml per mppcf, which has been observed in diverse environments such as mining and textile manufacture. This value was provisionally applied to this cohort.

The cohort consisted of 1074 white males who retired from the company during 1941-1967, and who were exposed to asbestos in production or maintenance jobs. The average duration of employment was 25 years. Followup started at age 65 or at retirement if work continued past age 65. By the end of followup in 1980, 88% were deceased.

Overall, respiratory cancer was significantly increased (SMR = 258 in comparison to U.S. rates, based on 79 observed deaths). Enterline *et al.* (1986) categorized lung cancer deaths by cumulative exposure (their Table 4). Results of applying the 1986 EPA lung cancer model to these data are shown in Table 20. Although both the model with $\alpha = 1$ and α variable fit the data adequately ($p \geq 0.75$), the test of $\alpha = 1$ was marginally significant ($p = 0.05$). With $\alpha = 1$ the estimate of KL was 0.0021 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0015,0.0027). With α variable, KL = 0.0011 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00041, 0.0028).

Since the test of the hypothesis $\alpha = 1$ was close to significance, KL was assumed to be the geometric means of the MLE estimates from $\alpha = 1$ and α variable. The uncertainty factors selected for this study were F1 = 2, F2 = 3, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

From the death certificates Enterline *et al.* identified eight deaths from mesothelioma. These data were not presented in a form that permitted application of the 1986 EPA mesothelioma model.

U.S. Insulation Applicators

Selikoff and Seidman (1991) reported on followup through 1986 of a cohort of 17,800 asbestos insulation applicators that had been followed through 1976 by Selikoff *et al.* (1979). The cohort consisted of men enrolled as members of the insulator's union in the United States and Canada. Deaths were classified both based on the information

the death certificate, and using "best evidence," in which death certificate information was augmented by clinical data, histopathological material and X-rays.

Based on the composition of insulation material, it seems likely that these workers were exposed to substantial amounts of chrysotile and amosite. Data on insulator's exposures were reviewed by Nicholson (1976), who concluded that average exposures of insulation workers in past years could have ranged 10-15 f/ml and could have been 15-20 f/ml in marine construction. USEPA (1986) assumed a value of 15 f/ml as an overall average, with an associated 3-fold uncertainty. This estimate of 15 f/ml will be used provisionally here as well.

The form of the data provided in Selikoff and Seidman (1991) is not particularly suitable for calculating KL. Table 4 of Selikoff and Seidman (1991) contain observed and expected deaths from lung cancer (determined from either death certificates or best information) categorized by years from first exposure (<15, 15-19, 20-24, ..., 50+). Death certificate information was utilized herein to facilitate comparisons with expected deaths (based on the mortality experience of U.S. white males), which were also based on death certificates. Lung cancer was significantly increased over expected, except for the category of < 15 years from onset of exposure. Selikoff and Seidman did not provide information on the duration of exposure. The USEPA (1986, page 90) assumed an average exposure duration of 25 years. Assuming that all workers worked exactly 25 years and were exposed to 15 f/ml, the data in Table 4 of Selikoff and Seidman (1991) can be used to categorize lung cancer deaths by cumulative exposure lagged 10 years. The result is shown in Table 21. The 1986 EPA lung cancer model provided a reasonable fit to these data with α variable ($p = 0.12$), but not with $\alpha = 1$ ($p < 0.01$). Also, the hypothesis that $\alpha = 1$ could be rejected ($p < 0.01$). The estimate of KL with α variable was 0.0018 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00065, 0.0038). With $\alpha = 1$, KL = 0.0087 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0081, 0.0093).

Although the hypothesis $\alpha = 1$ could be rejected, the estimated value of α (2.3) seemed somewhat large. Accordingly, the best estimate of KL was assumed to be the geometric means of the MLE estimates from $\alpha = 1$ and α variable. The uncertainty factors selected for this study were F1 = 4, F3 = 2 (no individual work histories) and F4L = 2 (data not summarized in appropriate form for fitting model), which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

Based on best evidence, Selikoff and Seidman (1991) found 458 mesotheliomas in this cohort. Table 22 shows these deaths categorized by years from onset (based on Selikoff and Seidman, 1991, Tables 5 and 6). Table 22 also shows the results of fitting the 1986 EPA mesothelioma model to these data, assuming, as above, that workers worked for 25 years and were exposed to 15 f/ml. The 1986 EPA mesothelioma model provided a poor fit to these data ($p < 0.01$), as it overestimates by more than a factor of 2 the number of mesothelioma deaths after 50+ years from first exposure. The

estimate of KM was $1.3x10^{-8}$, 90% CI: ($1.2x10^{-8}$, $1.4x10^{-8}$).

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors for exposure described earlier, when coupled with the statistical confidence limits, resulted in the likely range for KM shown in Table 1.

Pennsylvania Textile Plant

McDonald et al. (1983b) report on mortality in an asbestos plant located near Lancaster, Pennsylvania that produced mainly textiles, but also some friction materials. About 3,000 to 6,000 tons of chrysotile were processed annually at the plant, which began operation in the early 1900s. Crocidolite and amosite were used from 1924 onward; about three to five tons of raw crocidolite were processed annually and the use of amosite reached a peak of 600 tons during World War II.

The cohort consisted of all men employed for at least one month prior to 1959 and who had a valid record with the Social Security Administration. This group consisted of 4022 men, of whom 35% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only begun past 20 years from first employment.

To estimate exposures, McDonald et al. had available reports of surveys conducted by the Metropolitan Life Insurance Company during the period 1930-1939, Public Health Service surveys conducted during 1967 and 1970, and company measurements made routinely from 1956 onward. These data were used to estimate by department and year in units of mppcf.

The lung cancer mortality in this cohort exhibited a significant dose response trend (Table 23), which was partially due to a deficit of cancers in the group exposed to <10 mppcf-y (21 with 31.4 expected). A survey of those employed in the plant in 1978 revealed a larger per cent of nonsmokers (25%) than were found in the other plants studied by these researchers (McDonald et al., 1983a,1984), although this finding was based on a sample of only 36 workers. Regardless of the reason for this shortfall in the number of lung cancers, it appears that the most appropriate analysis is that in which the background is allowed to vary; this analysis fits the data well ($p > 0.7$), whereas the analysis which assumes the Pennsylvania rates are appropriate provides a marginal fit ($p = 0.08$). The hypothesis $\alpha = 1$ was rejected ($p < 0.01$). Consequently, the former analysis is judged to be the most appropriate (allowing the parameter α to vary). McDonald *et al.* did not provide a factor for converting from mppcf to f/ml. Assuming that 3 f/ml is equivalent to one mppcf, the resulting estimate of lung cancer potency with α variable was 0.018 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0075, 0.045). With $\alpha = 1$, KL = 0.0057 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0027, 0.0094).

The best estimate of KL was assumed to be from the analysis with α variable. The uncertainty factors selected for this study were F1 = 2, F2 = 3, which, when coupled with the statistical confidence limits, resulted in the likely range for KL shown in Table 1.

A diagnosis of mesothelioma was specified on fourteen death certificates (ten pleural and four peritoneal). Thirty other deaths were given the ICD code 199 (malignant neoplasms of other and unspecified sites) and the diagnosis given in many of these cases was said to be consistent with an unrecognized mesothelioma. McDonald et al.'s Table 3 lists the average age at beginning of employment as 28.92 and the average duration of employment as 9.18 years, and their Table 1 lists 191, 667 and 534 deaths as occurring before age 45, between 45 and 65, and after 65 years of age, respectively. Assuming that 1/2 of the deaths given the ICD code 199 might have been due to mesotheliomas, the total number of mesotheliomas in this cohort is estimated to be 23. Proceeding as in the mesothelioma analysis carried out for the McDonald et al. (1984) data, the data in Table 24 were generated. Noting that the age since first exposure categories in which the mesotheliomas occurred is irrelevant as far as estimating KM is concerned, the estimate of KM is 1.1×10^{-8}, 90% CI: (0.76×10^{-8}, 1.5×10^{-8}). These estimates are uncertain due to the uncertainty regarding the number of mesotheliomas in the cohort.

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits and an additional uncertainty factor (F4M = 2) to account for uncertainty in the number of mesotheliomas, resulted in the likely range for KM shown in Table 1.

Rochdale, England Textile Factory

Peto et al. (1985) studied a textile factory in Rochdale, England that has been the subject of a number of earlier reports (Peto, *et al.*, 1977; Peto, 1980a,b). Peto *et al.* (1985) has the most complete follow-up (through 1983) and emphasizes assessment of risk. The factory, which began working with asbestos in 1879, used principally chrysotile, but approximately five percent crocidolite was used between 1932 and 1968.

Quantitative estimates of risk were based on a subgroup of Peto et al.'s "principal cohort" consisting of all men first employed in 1933 or later who had worked in scheduled areas or on maintenance and had completed five years of service by the end of 1974. In the analyses of interest relating to lung cancer, follow-up only begins 20 years after the beginning of employment and exposure during the last five years of follow-up is not counted.

Routine sampling using a thermal precipitator began at 23 fixed sampling points in 1951. Comparisons of particle counts and fiber counts taken in 1960 and 1961 were

used to convert between particles/ml and f/ml. Dust levels prior to 1951 were assumed to be the same as those observed during 1951-1955 for departments for which no major changes had been made. In departments in which conditions had improved, higher levels were assigned. These levels and work histories were used to assign individual exposure estimates. A conversion factor of 34 particles/ml per f/ml was determined by comparing average results obtained by the Casella thermal precipitator (particles/ml) with Ottway long running thermal precipitator (f/ml) at the same sampling point during 1960 and 1961. However, a conversion factor of 35.3 was used by Peto et al. for the sake of consistency with earlier work, and this factor will be used here as well.

After 20 years from first employment, there were 93 lung cancer deaths with only 64.6 expected. Using a lung cancer model essentially the same as the 1986 EPA model, Peto et al. estimated KL = 0.0054 $(\text{f-y/ml})^{-1}$ for the entire cohort, and KL = 0.015 $(\text{f-y/ml})^{-1}$ when the analysis was restricted to men first employed in 1951 or later. Peto et al. felt that the most plausible explanation for this difference was that it was largely due to chance and also possibly to the chance that exposure to the most carcinogenic fibers was not reduced as much as changes in particle counts from 1951 and 1960 would suggest.

The best estimate of KL was assumed to be the geometric mean of the two estimates obtained by Peto *et al.* Since Peto *et al.* did not provide confidence intervals, the upper and lower statistical bounds were assumed to be equal to the larger and smaller of the two estimates, respectively, with an additional uncertainty factor added (F4M = 2). The best estimate of KL was assumed to be from the analysis with α variable. The remaining uncertainty factors selected for this study were F1 = 2, F3 = 2, which resulted in the likely range for KL shown in Table 1.

Ten mesotheliomas were observed in the cohort used by Peto et al. for quantitative analysis (an eleventh case who was exposed for four months and died four years later was omitted because the short latency made it unlikely that this case was related to exposure at the factory). Observed mesotheliomas and corresponding person years of observation by duration of service and years since first employment (Peto *et al.*, 1985, Table 8) are shown in Table 25. An overall average exposure was estimated by applying the Peto mesothelioma model to the data in Table 25 with a single exposure estimate selecting the value that gave the smallest least squares fit of this model to the mesothelioma data. The fitting was carried out both unweighted and by weighting by the person years, with resulting estimates of 360 and 322 particles/ml, respectively; the latter value was the one selected. Using the conversion factor of 35.3 particles/ml per f/ml, the estimated average exposure is 322/35.2 = 9.1 f/ml. The 1986 EPA mesothelioma model fit these data well (p = 0.80), and the resulting estimate of mesothelioma potency (Table 25) was KM = 1.3×10^{-8}, 90% CI: (0.74x10-8, 2.1×10^{-8}).

The MLE estimate of KM was assumed to be the best estimate. The uncertainty factors described earlier, when coupled with the statistical confidence limits, resulted in the likely range for KM shown in Table 1.

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